Origins of Autoacceleration in L-proline-assisted Aldol-type Reactions

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The formation of complex hydrocarbons from smaller molecules is very important to the pharmaceutical, petrochemical, and agricultural industries. Petroleum refining supplies only a limited number of paraffins, naphthenes, and aromatic components. Therefore, aldol, oxyamination, and amination reactions, processes that create new carbon-carbon and carbon-heteroatom bonds, are of major significance. Currently, strong acids and bases, transition metals, and heterogeneous materials catalyze such reactions. In recent years, a major challenge in industrial chemistry has been the switch to more ecologically friendly syntheses. As a consequence, organocatalysts have emerged as potential substitutes for traditional catalysts.

L-proline, an amino acid, has been demonstrated to catalyze a variety of bond-forming reactions under homogeneous conditions without the need for modification of the carbonyl compounds. Moreover, the strength of L-proline as a catalyst lies in the fact that it is inexpensive, operates at low temperatures, and exhibits a high yield and atom efficiency. Nevertheless, there exists a practical limitation to the use of L-proline as a catalyst. Most proline-assisted aldol reactions require long reaction times and are characterized by low turnover number. Recently, auto-inductive behavior has been observed in a-aminoxylation and a-amination reactions promoted by L-proline. As a result, these reactions occur on the time scale of minutes or hours. Experimental kinetics techniques are unable to pinpoint definitively the nature of the rate-enhancing interactions in the catalytic cycle of these reactions. To date, all L-proline assisted aldol-type reactions are considered to proceed via the same biomimetic catalytic cycle involving the formation of an enamine intermediate. As a first step towards understanding the origin of the kinetic behavior of L-proline-catalyzed reactions, we are using ab initio methods to explore the differences between an aldol addition and an a-aminoxylation reaction at the atomistic level. All stable intermediates and transition states along the reaction coordinates were located using the Gaussian 03 computational chemistry software. In order to identify the rate-limiting step in each process, microkinetic models were developed employing rate parameters calculated from the quantum chemical results and standard statistical thermodynamics methods. As a result, we are able to identify the possible origins of the observed autoacceleration as well as prescribe targets for catalyst improvement.